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Migraine and cognitive decline: A topical review

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Abstract

Migraine has been linked with an increased risk of stroke and an increased prevalence of clinically silent brain lesions and white matter hyperintensities. As it is known that stroke and structural brain lesions are associated with an increased risk of cognitive decline, it has been hypothesized that migraine may be a progressive brain disorder and associated with an increased risk of cognitive impairment. Given the prevalence of migraine in the population, especially among women, and the aging of the population, an association between migraine and cognitive impairment would have substantial public health implications. In this review, we will summarize the existing evidence evaluating the association between migraine and cognitive function. Additionally, we will discuss methodological issues in migraine and cognitive function assessment and elaborate on study design strategies to address this important question.

Keywords

migraine; cognitive decline; epidemiology

Introduction

Migraine is primarily a disorder of the brain with a strong vascular involvement. Over the last decades, several studies have linked migraine with increased risk of stroke.^{1, 2} In addition, migraine has been associated with an increased prevalence of clinically silent brain lesions^{3–6} and a meta-analysis found a nearly four-fold increase in the risk of white matter abnormalities among those who experience migraine.⁷ Recent findings from the Cerebral Abnormalities in Migraine, an Epidemiological Risk Analysis Cohort (CAMERA II) study showed that migraine may lead to progression of deep white matter lesions.⁸ Moreover, results of a small study suggest that patients with migraine have decreased frontal and parietal lobe gray matter density and slower response time to task set-shifting.⁹ Taken together, these findings suggest that at least in some patients with migraine structural brain lesions exist. As stroke and white matter hyperintensities have been associated with

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increased risk of dementia,¹⁰ it can be hypothesized that individuals with migraine have impaired cognitive function. Due to the high life time prevalence of migraine in the general population and an increasing life expectancy, a causal association between migraine and cognitive impairment would have major public health consequences. These consequences would be especially important among women who have a higher prevalence of migraine¹¹ and dementia¹² compared to men.

In this review, we will summarize the existing evidence evaluating the association between migraine and cognitive function. We will discuss methodological issues in migraine and cognitive function assessment and elaborate on study design strategies to address this important question.

Methodological Considerations

When evaluating the association between migraine and cognitive decline, several methodological options can be considered: source populations, assessments of migraine and cognitive function, and major study designs.

Source population

Two main types of study populations are considered in the migraine-cognitive decline assessment: clinic-based and population-based. Clinic-based samples are in general easier to assess, have good disease classification, and, as individuals usually have a medical condition, they are more likely to participate in scientific studies. However, participants from clinic-based settings may have a more severe disease condition and/or other medical conditions that bring them into the clinic which often are related to the outcome event of interest. In addition, a control group that is entirely unrelated to the outcome of interest is difficult to identify. While population-based studies have several advantages (generalizability, large size, often with follow-up data), difficulties occur in disease classification as investigators have to rely on standardized often self-reported assessment tools. For the specific migraine-cognitive decline example there are some specific concerns. While clinic-based samples may often have confirmed clinician diagnosis of migraine and more detailed information on migraine characteristics, these studies may be vulnerable to selection bias.¹³ For example, patients who seek treatment in headache clinics may have more severe migraine features than patients with migraine in the general population. If migraine's effects on cognitive function primarily act through migraine severity, such as increased attack frequency, findings from clinic-based population will not reflect the association in a population-based setting. Additionally, patients with migraine seeking treatment in clinics have higher levels of anxiety compared to controls.¹³ As anxiety is also linked to cognition, associations between migraine and cognitive decline may be biased.

Classification

The International Headache Classification (ICHD-I and ICHD-II) provides clear criteria for diagnosing migraine. However, migraine assessment differs considerably depending on the population studied. In general, migraine can be either self-reported or physician diagnosed. Often in large cohort studies, it is not feasible to have physicians evaluate all subjects for migraine, so these studies often rely on self-reported migraine and perform validation studies to determine the validity of their self-reported migraine measure. However, misclassification of some subjects is still possible, which can either lead to random or non-random bias.

In contrast to the standard criteria for diagnosing migraine, no universal standard for measuring cognitive decline exists. The wide variety of tests available and the different domains assessed by these tests can make comparing results between different studies

difficult. Additionally, some commonly used measures, like the Mini-Mental State Examination, may not be sensitive enough to pick up small changes in cognitive functioning. However, tests like the MMSE are often easier to implement to large cohort studies than an exhaustive panel of cognitive tests.

Study design

When studying the association between migraine and cognition, only few study designs are applicable. In particular, retrospective case-control studies are hardly feasible when cognitive decline is the outcome as patients with impaired cognitive function will not adequately recall migraine history. Thus, the main study designs used to evaluate the question whether migraine leads to cognitive decline are cross-sectional or longitudinal studies.

Cross-sectional studies

Several studies have looked at the associating between migraine status and cognitive function but results from these studies are mixed. Some cross-sectional studies found no differences between migraineurs and non-migraineurs controls^{13–17} while others found evidence of worse cognitive performance among migraineurs compared to non-migraineurs controls.^{18–22} One cross-sectional study looked at cognitive performance just among migraineurs and found that attack frequency was not related to cognitive performance.²⁰ However, there was some evidence that the location of pain (right side, left side or bilateral) may impact immediate and delayed recall on the Rey Complex Figure Test. Among migraineurs with aura, those with right-sided and bilateral pain exhibited the worst recall. Among migraineurs without aura, only those with bilateral pain exhibited the worst recall.

While most of the cross-sectional studies have been small, some larger studies have been performed. One cross-sectional study used data from 99 migraineurs and 1768 people without migraine participating in the Maastricht Aging Study.¹⁵ Migraine status was self-reported and the Letter Digit Substitution Test and the Verbal Learning Test and Delayed Recall were used to assess cognitive function. Those with migraine did not have significantly lower scores on these tests. The authors were unable to stratify their results by migraine aura status.

Another study enrolled 74 migraineurs (45 of whom experienced migraine with aura) and 74 age- and sex-matched non-migraineurs to determine if migraine status was associated with lower scores on the AH4 test, which examined fluid intelligence, the Mill Hill Vocabulary test and the Digit Symbol Substitution test for processing speed.¹⁷ Migraineurs with and without aura did not performed worse on any of the cognitive tests and the effect of age on cognitive performance did not seem to vary across migraine groups.

One of the largest cross-sectional studies used data from the Danish Twin Registry and enrolled 1393 twins, 536 of which had migraine diagnosed by a neurology (347 migraine without aura and 157 migraine with aura).¹⁴ They found that the average cognitive scores on fluency, digit span, delayed word recall, and symbol digit substitution test did not differ for migraineurs overall, migraineurs with aura and migraineurs without aura compared to non-migraineurs. Additionally they did not find evidence that cumulative number of migraine without aura attacks, age at migraine onset or number of years of migraine attacks impacted the lack of association between migraine and cognitive functioning.

A small study of 61 participants with migraine, 50 participants with non-migraine headache and 367 headache-free controls did not observe differences in cognitive functioning between those without any headache, those with non-migraine headache and those with migraine on

most cognitive functioning tests. For two cognitive tests, those with non-migraine headache performed the worst which the authors suggest may mean that the cognitive impact of migraine is not specific to migraine but may be associated with headache.²³

While cross-sectional studies helped to raise the hypothesis that migraine may not be associated with cognitive decline, there are several limitations to these studies. First, all of these studies did not assess change in cognitive functioning over time. Because dementia is often preceded by changes in cognitive functioning over time, research into cognitive functioning now focuses on finding factors that may impact change in cognitive functioning over time. Second, many of these studies were small which may limit their ability to detect small differences amongst those with and without migraine. Additionally, some studies did not show results separately for all migraineurs, migraineurs with aura and migraineurs without aura.^{13, 15, 22, 23} Given the differences in risk of stroke and cardiovascular disease (CVD) that have been observed for migraineurs with and without aura, it is plausible that cognitive function may also vary between those with and without aura. Finally, all or most of the migraineurs in some studies were recruited from clinics^{16, 18, 19, 22, 23} and it has been suggested that some of the discrepant results between studies could be explained by selection bias or higher levels of anxiety among clinic patients.¹³

Longitudinal Studies

One of the main advantages of using a longitudinal study design is that these studies can specifically address whether migraine is associated with cognitive decline over time. Four longitudinal studies have been performed that assess the association between migraine and cognitive decline in adults (see Table 1) using data from the Maastricht Aging Study (MAAS),²⁴ the Baltimore Epidemiologic Catchment Area Study (ECA),²⁵ the Epidemiology of Vascular Ageing Study (EVA)²⁶ and the Women's Health Study (WHS).²⁷ Unlike some of the cross-sectional studies, all of the longitudinal studies have used population-based samples.

Migraine Assessment in longitudinal studies

Three studies assessed migraine through a series of questions based on the ICHD-I or modified ICHD-II criteria.^{25–27} The remaining study only asked participants whether a doctor had diagnosed them as having migraine headaches.²⁴ Three studies assessed whether their participants experienced migraine with aura.^{25–27} One study had an additional migraine category of “past history of migraine” which was defined as women who had experienced migraine in the past, but did not experience migraine in the year prior to baseline.²⁷ Another study also examined whether severe headache was associated with cognitive decline.²⁶

Cognitive Assessment in longitudinal studies

Although the number of tests used varied across studies, all studies assessed global cognitive function using either the Mini-Mental State Examination or the Telephone Interview for Cognitive Status, a telephone adaptation of the MMSE, and assessed immediate and delayed recall through the use of the Rey Verbal Learning Test or the East Boston Memory Test.

For all studies, participants were assessed at baseline and then at least once during follow-up. Participants in EVA were assessed three times during follow-up²⁶ and participants in WHS were assessed twice during follow-up.²⁷ Average follow-up ranged from a mean of 3.4 in WHS²⁷ to approximately 12 years in the Baltimore Epidemiology of Vascular Aging Study.²⁵

Results for Overall Migraine

Three studies presented results for the association between any migraine and cognitive decline over time (Table 2).^{24–26} To test for this effect, all studies included an interaction term between migraine and time in their longitudinal models. The MAAS did not find any evidence that migraine was associated with significantly faster decline over time (all p-values >0.05) compared to those without migraine in any of their cognitive tests.²⁴ Except for the Wechsler text, the EVA study also did not find evidence that migraine was associated with faster decline over time.²⁶ In the Wechsler test, migraineurs may experience significantly less decline over time than those without severe headache (p=0.02). The ECA study found that migraineurs may exhibit significantly less decline over time in tests of immediate and delayed recall compared to those without migraine.²⁵ There was no difference in the rate of decline in the MMSE between migraineurs and non-migraineurs.

Results from these three studies suggest that migraine is not associated with greater cognitive decline over time and may even be associated with less decline over time in some tests. However, this result was not consistently found across all studies and cognitive tests.

Migraine Subtypes

Since migraine with aura in particular has been linked to an increase risk of ischemic stroke, it is important to consider whether the association between migraine and cognitive decline may vary based on aura status. Although three studies assessed whether their participants experienced migraine with aura,^{25–27} only two studies had enough participants who experience migraine with aura to able to present results on the longitudinal association between migraine with aura and cognitive decline (Table 2). The WHS showed no association between migraine with aura and decline in any of their cognitive assessments (all p-values = 0.05).²⁷ The ECA study showed a similar result for migraineurs with aura as they showed for migraine overall.²⁵ For tests of immediate and delayed recall, people who experience migraine with aura had significantly less decline than those without any migraine while for the MMSE there was no difference in the rate of decline between those who experience migraine with aura and those without any migraine.

Both WHS and ECA also examined whether migraine without aura was associated with cognitive decline and found no differences in decline between those who experience migraine without aura and those who do not experience any migraine.^{25, 27} The WHS additionally had a “past history of migraine category” which was defined as women who had experienced migraine in the past, but did not experience migraine in the year prior to baseline. The women with a past history of migraine were also not at increased risk of cognitive decline compared to women without any history of migraine.²⁷

Although the EVA study was unable to display separate longitudinal results for migraineurs with and without aura, this study did examine whether non-migraine headache was associated with cognitive decline over time. They found no evidence that migraine headache was associated with increased cognitive decline compared to those without any headache.²⁶

Effect Modification by Gender

Three studies enrolled both men and women and examined whether the association between migraine and cognitive decline may be modified by gender.^{24–26} As expected, in all three studies, the proportion of men who experience migraine was lower than the proportion of women who experience migraine. Although three studies enrolled both men and women, only EVA and ECA specifically tested for effect modification by gender. Both EVA and ECA found no evidence of effect modification by gender of the association between migraine and cognitive decline.^{25, 26} The EVA study did find some evidence that men who

experience non-migraine headache decline less than women who experience non-migraine in the Raven test. However, this result was not observed for any other cognitive test.

Effect Modification by Age

Three studies tested whether the effect of migraine on cognitive decline may vary based on the age of the participant.^{25–27} Although all studies dichotomized age around the mean or median for their cohort, the three studies had fairly different age distributions and therefore used different absolute cutpoints. In the EVA study, age was dichotomized at 69 years of age and they found no evidence that age modified the effect of migraine on cognitive decline for any of their cognitive tests.²⁶ The WHS had the oldest age distribution and dichotomized age at 75 years.²⁷ The association between migraine and cognitive decline was not modified by age on most cognitive tests. For the telephone interview for cognitive status, there was some evidence of effect modification by age. However, this result appeared to be driven by one time point and the past history of migraine group. At the third time point, those who were older than 75 years and had a past history of migraine appeared to have a greater rate of cognitive decline compared to those younger than 75 years with a past history of migraine.

While the two older cohorts did not find much evidence of effect modification by age, the ECA study, with a mean age of 52 years and a median age of 47 years) did observe effect modification by age.²⁵ They found that among those younger than 50 years of age migraine and migraine with aura were not associated with cognitive decline over time. Among those 50 years of age or older, migraine with aura was associated with less decline over time (0.99 points on the MMSE less per year compared to those without migraine).

Effect Modification by Education or Baseline Cognitive Status

The ECA and WHS, the only studies that examined effect modification by educational attainment and baseline cognitive score, did not find any evidence that education attainment or baseline cognitive score modified the association between migraine status and any of their cognitive tests.^{25, 27}

Effect Modification by Genetic Factors

The ECA study had information on *APOE ε4* carrier status while EVA had information on *APOE ε4* carrier status and *MTHFR* genotype. *APOE ε4* carrier status has been linked to an increased risk of Alzheimer's disease²⁸ while *MTHFR* genotype has been associated with migraine status.²⁹ However, neither study found evidence that either genetic factor modified the association between migraine and cognitive decline.^{25, 26}

Effect Modification by Medication Use

The ECA study specifically tested for effect modification by non-aspirin nonsteroidal anti-inflammatory drug (NSAID) use and found no evidence that non-aspirin NSAID use modified the association between migraine and cognitive decline.²⁵ The MAAS study asked participants about all medications used on a regular basis and the effects of specific medication and non-specific medications on cognitive functioning were tested. They found that specific and non-specific medication use did not result in increased or decreased cognitive decline in migraineurs.²⁴

Other than direct information on modification of the association between migraine and cognitive decline by specific medications, it is also important to bear in mind that some migraine prophylactic medications, such as topiramate³⁰ or comorbid conditions, such as depression³¹ and chronification of migraine³² can potentially lead to symptoms of cognitive dysfunction and slower thought process.

Effect Modification by Structural Brain Lesions

Previous studies have shown that migraine and cognitive decline are both associated with an increased prevalence of white matter hypertensities.^{3–7} Although most studies did not have MRI information on their participants, the EVA study and the CAMERA-2 study did have MRI and cognitive decline information for migraineurs and non-migraineurs.^{8, 26} Using data from 775 participants in the EVA study with available MRI data, the presence of any brain infarct (yes/no) and total white matter hyperintensity (highest tertile versus two lowest tertiles) did not modified the association between migraine and cognitive decline for most cognitive tests.²⁶ The interaction between migraine, time and brain infarctions was of borderline significance ($p=0.06$) for the Wechsler test. Analyses stratified by the presence or absence of brain infarcts revealed that among those without brain infarcts, non-migraineurs decline faster than migraineurs. However, among those with brain infarcts, migraineurs decline faster than non-migraineurs. The p -value for the three way interaction between migraine, time and total white matter hyperintensity was of borderline significance for the Raven test ($p=0.06$) and stratified analyses indicated that migraineurs with low total white matter hyperintensity load may experience more decline than those with high load. This result is unexpected since high white matter hyperintensity load has been associated with cognitive impairment.

Recent longitudinal results from the CAMERA-2 study found no difference between migraineurs and controls after 8.5 years of follow-up. Additionally, deep white matter hyperintensity load was not associated with cognitive performance over time and presence of migraine did not influence the lack of association (p -value=0.30).⁸

Given the results from the EVA and CAMERA-2 studies, the presence of brain infarctions or high white matter hyperintensity load do not seem to result in increased cognitive decline among those who experience migraine with aura compared to those who do not experience migraine.

Effect Modification by the Occurrence of CVD Events

Migraine, particularly migraine with aura, has been associated with an increased risk of ischemic stroke.² Previous research in the WHS has additionally shown associations between migraine with aura and overall CVD, ischemic stroke, myocardial infarction, coronary revascularization, angina and ischemic CVD death.³³ Given the associations between migraine and CVD and the increased risk of dementia among those with stroke³⁴, it is plausible that the occurrence of CVD events may modify the association between migraine and cognitive decline. Of the four longitudinal studies on migraine and cognitive decline, only the WHS tested for effect modification by CVD events. They found that for the category fluency test among those women who experienced migraine with aura, those who experienced a CVD event had greater rates of decline during follow-up than those who did not experience a CVD event.²⁷ However, they did not observe effect modification by the presence of CVD event for any other other cognitive test. Future studies need to examine whether the occurrence of CVD events and the particular type of CVD event may modify the association between migraine and cognitive decline.

Rare subtypes of migraine and cognition—There are rare subtypes of migraine and distinct syndromes that have migraine as a feature which have been associated with impaired cognitive function. For example, a small study of patients with familial hemiplegic migraine found persistent cognitive deficits.³⁵ Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an inherited small-artery disease of mid-adulthood caused by specific genetic mutations. The disease is responsible for widespread white-matter lesions associated with lacunar infarctions in various

subcortical areas and migraine is part of the disease symptomatology.³⁶ Results of some studies data suggest that the number of lacunar infarctions and severity of cerebral atrophy are the main magnetic resonance imaging markers associated with cognitive disabilities.³⁷ Patients with mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) also have severe migrainous symptoms.³⁸ In a study of 10 patients, a rate of cognitive regression could be observed that reflected the rapidity of disease progression.³⁹ However, on the population level, these migraine subtypes and distinct syndromes are very rare.

Summary

Results from longitudinal studies on migraine and cognitive decline consistently show that those who experience any migraine, migraine with aura or migraine without aura are not at increased risk of cognitive decline. Most studies did not find meaningful modification of the lack of association between migraine and cognitive decline by gender, education, baseline cognitive status, *APOE* or *MTHFT* genotype and medication use. Except for one study, most longitudinal studies did not find evidence of effect modification by age.

Despite the associations seen between migraine and structural brain lesions in previous studies, two studies with information on migraine, structural brain lesions and cognitive functioning did not find strong evidence of worse cognitive performance among migraineurs with high structural brain lesion load. This suggests that while migraine may be associated with structural brain lesions, these lesions are not related to cognitive decline. However, the number of patients with both migraine and structural brain lesions was small in both of these studies which may have impacted the ability to detect associations between migraine, structural brain lesions and small changes in cognitive functioning.

The lack of association between migraine and cognitive decline should provide reassuring evidence for migraine patients and their treating physicians. While cerebrovascular disease is associated with cognitive decline, it is not yet known if migraine may further exacerbate the deleterious effect of cerebrovascular disease on cognitive function. Most of the studies evaluating the association between migraine and cognitive decline had limited information on migraine specifics including attack frequency. Future studies should determine if specific migraine characteristics, for example attack frequency, may impact the association between migraine and cognitive decline.

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Abbreviations

CAMERA-II	Cerebral Abnormalities in Migraine, an Epidemiological Risk Analysis cohort
ICHD-I and ICHD-II	International Headache Classification I and II
MMSE	Mini-Mental State Examination
CVD	cardiovascular disease
MAAS	Masstricht Aging Study
ECA	Baltimore Epidemiologic Catchment Area Study
EVA	Epidemiology of Vascular Ageing Study

WHS	Women's Health Study
APOE	apolipoprotein E
MTHFR	methylenetetrahydrofolate reductase
NSAID	non-steroidal anti-inflammatory drug

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Table 1

Characteristics of longitudinal studies included in this review.

Study (Reference)	Country	Source Population	Number of subjects	Mean Age	Gender	Migraine Diagnosis	Migraine status investigated	Length of follow-up	Cognitive measures used
Kalaydjian 2007	US	Baltimore Epidemiologic Catchment Area Study (ECA)	204 migraineurs (95 with aura) 1244 non-migraineurs	47.5±12.5 in migraineurs 52.7±15.7 in non-migraineurs	Men and women	Self-report on questionnaire (IHS criteria 1988)	Overall migraine, migraine with aura	~12 years	MMSE Immediate and delayed recall (Rey)
Baars 2010	Netherlands	Maastricht Aging Study (MAAS)	99 migraineurs 1724 non-migraineurs	47.1±12.9 in migraineurs 51.8±16.6 in non-migraineurs	Men and women	Self-report of doctor diagnosis	Overall migraine	6 years	Immediate word recall Delayed word recall MMSE Stroop inference Letter Digit Substitution test
Rist 2011	France	Epidemiology of Vascular Ageing Study (EVA)	167 migraine (24 with aura) 65 non-migraine headache 938 no severe headache	69.0±2.9 migraine 69.3±3.1 non-migraine headache 68.9±3.0 no severe headache	Men and women	Telephone interview with a neurologist (modified ICHD-II criteria)	Overall migraine, non-migraine headache	4–5 years	MMSE Digit Symbol Substitution Test from the Wechsler Trial Making A Trial Making B Rey Raven Benton Finger Tapping Word Fluency
Rist 2012	US	Women’s Health Study (WHS)	195 MA 248 MO 410 Past history of migraine 5496 no history of migraine	65.9±3.9 MA 65.3±3.6 MO 66.4±4.1 Past history of migraine 66.3±4.1 no history of migraine	Women	Self-report on questionnaire (modified ICHD-II criteria)	MA, MO, Past history of migraine	Mean of 3.4 years	Global score* Verbal score** TICS Category fluency test

* Global score includes TICS, immediate and delayed recall trials of the east Boston memory test, delayed recall trial of the TICS 10 word list and a category fluency task

** Verbal Score includes immediate and delayed recalls of the east Boston memory test and the TICS 10 word list

Table 2

Multivariate-adjusted associations between rate of change in cognitive function as measured by the MMSE or TICS* and migraine status.

Study	Coefficient and Standard error or confidence interval**
ECA	
Time	-0.28 (-0.43, -0.12)
Migraine	0.24 (0.01, 0.46)
Migraine × time	0.11 (-0.17, 0.38)
MAAS	
Time	0.28 (0.14, 0.42)
Migraine	0.52 (-0.32, 1.37)
Migraine × time	-0.35 (-0.86, 0.16)
EVA	
Time	0.24 (0.03)
Migraine	0.28 (0.21)
Migraine × time	-0.01 (0.07)
Headache	0.33 (0.32)
Headache × time	-0.04 (0.10)
WHS	
Second time point	-0.11 (0.04)
Third time point	-0.12 (0.04)
MA	0.04 (0.18)
MA × Second time point	-0.11 (0.21)
MA × Third time point	-0.11 (0.22)
MO	0.07 (0.16)
MO × Second time point	0.09 (0.19)
MO × Third time point	0.25 (0.20)
Past history of migraine	0.29 (0.13)
Past history of migraine × Second time point	-0.24 (0.16)
Past history of migraine × Third time point	-0.13 (0.16)

* The WHS used the TICS instead of the MMSE. All other studies used the MMSE.

** The EVA and MAAS presented beta-coefficients and confidence intervals. The EVA and WHS presented beta-coefficients and standard errors.